DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852 1448

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CBER – 02 – 017

Warning Letter

SEP 27 2002

Harry D Bear, M D , Ph.D
Virginia Commonwealth University
1200 East Broad Street
W Hospital Room 7-408
Richmond, Virginia 23298-0011

Dear Dr Bear

During an inspection that ended on April 29, 2002, Candice Cortes, an investigator with the Food and Drug Administration (FDA), reviewed your activities as a clinical investigator testing an investigational melanoma vaccine in study ———— The inspection was conducted as part of the FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational drugs

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Part 312 (available at http://www access gpo gov/nara/cfr/index html) The applicable provisions of the CFR are cited for each violation listed below.

We reviewed your May 13, 2002, response to the Form FDA 483 issued to you at the close of the inspection Although a number of the corrections you describe or propose appear to be adequate, it is essential that you ensure they are fully implemented immediately and that you monitor them to ensure they achieve their intended purposes Some of your responses, however, appear inadequate or contain justifications with which we do not agree, as noted specifically below

1. **You failed to ensure that the investigation is conducted according to the investigational plan. [21 CFR § 312.60].**

   A Protocol section 11 1 4 states. "...it is important that the individual preparing the study drugs must be someone other than the person administering the vaccine" and "It will still be necessary, however, for the investigational agent to be reconstituted and blinded by a third party who will have no role in the management of the patient or assessment of toxicity

Contrary to these protocol requirements, for eight of the —— subjects enrolled in the study, Dr. —— both prepared the study drug and had a role in subject management and in the assessment of toxicity. Specifically, Dr. ——

- conducted study visit assessments on the following dates during which he managed subjects and assessed toxicity, even though he had also prepared the study drug:

Subject	Date
	4/29/99
	8/29/00, 9/26/00
	8/29/00
	8/29/00
	8/29/00, 9/12/00, 9/26/00
	12/28/00
	1/2/01

- reviewed adverse event reports and signed the case report form on the line designated for the clinical investigator for subjects —— (on 4/24/99 and 12/8/99), —— (on 9/21/00), and —— (on 11/6/00).

- signed the case report form on the line designated for the clinical investigator for the "End of Study" form for subject ——

- signed as the person who administered the study drug to subjects —— on 4/29/99 and —— on 8/29/00. There was no nurse's signature on these case report form pages.

  Your response letter explains that all doses were administered by a research nurse, but that cannot be verified from these records. You also explained that the current version of the case report form page for study visit assessments now has a signature lines for the nurse administering the test article.

Your response letter states that Dr. —— (a) did not participate in the management of subjects or the assessment of toxicities since September 2000 and (b) will not participate in these activities in the future. We note that, as seen in the table above, Dr. —— conducted study assessments through January 2001. As a result of his activities beyond preparing the study drugs, the study blind was compromised for the subjects listed above. As the clinical investigator of the study, you are responsible to ensure that the study blind is maintained by keeping the study drug preparation duties separate from care of the subjects.

These errors reflect a pattern of insufficient training and experience that may impact the safety and welfare of subjects, and the ability to determine the safety and efficacy of the study drug..

Throughout your response letter you refer to the persons who prepare the study drugs as "pharmacists." We note that, as of the conclusion of the inspection, the individuals who have prepared study drugs have not been registered pharmacists qualified by training and experience.

B. Several study visits were conducted by personnel not medically qualified to evaluate the subjects' disease status, including the study coordinator and Dr. ——— (who also should have abstained from such evaluation because he is the study drug preparer). .

C. You administered expired study drugs and skin test reagents to subjects. ——— skin test reagent expired — days after opening the vial. The protocol and "Pharmacy Manual" require that expired study drug is not to be used.

Test article or Skin test reagent	Expiration Date	Administration Date	Subject
—	12/8/99	12/21/99, 1/18/00	
—	5/5/00	5/9/00, 6/20/00 8/15/00	
—	6/1/01	6/7/01	
—	4/5/01	5/8/01	
—	8/25/00	8/29/00 9/28/00 11/9/00 11/21/00 12/5/00 1/9/01	
—	7/8/99	8/3/99 10/5/99 11/9/99 11/18/99 12/14/99 12/28/99 1/28/00 2/1/00	
—	9/2/99	10/5/99 11/9/99 12/14/99	

In your response, you provided a memorandum documenting that the sponsor extended the expiration date for several lots of the test article. However, the sponsor did not extend the expiration date for any of the test article lots listed in the table above. You also explain that the —— vial does not indicate that it expires — days after opening. We note, however, that this information is found in the manufacturer's package insert and in the "Pharmacy Manual" provided by the sponsor. Your response states that these errors were unintentional and isolated events. Your response also states that you have re-trained the person preparing the study drugs. It is your responsibility to monitor all personnel to ensure that they are following all protocol requirements and established procedures.

D. The protocol's "Site Reference Manual" states, "Laboratory test results must be initialed and dated by the Investigator indicating that they were reviewed." There are several examples of laboratory reports that were not signed or dated by you or a sub-investigator responsible to you.

Your response letter states that in the future a qualified investigator will review and initial laboratory test results, and that you have re-trained your study team to follow the protocol requirements. Your response does not explain how you will ensure that these procedures have been properly executed or completed.

E. The study coordinator signed the "Request to Transfer Patient" form to accept the transfer of subject —— even though the "Site Reference Manual" requires that "the investigator must review and sign the form accepting the transfer." You signed this form approximately 18 months after the transfer occurred.

Your response letter states that you will sign these forms in the future.

F. The "Site Reference Manual" requires that "the depth of the ——— should be measured and recorded at least ——— (emphasis in original). The "Pharmacy Manual" "recommend[s] measuring and recording the level of ——— and the internal temperature ———." There are no records of the——— levels for 1999 and 2000.

Your response acknowledges that records for refilling of the ——— tank are missing for 1999 and 2000, although you "are confident" that the ——— freezer was properly maintained during that period. You also state that you have been using a new form, supplied by the sponsor 1/21/2002, to document refilling of the freezer.

G. The sponsor provided a log sheet, on which all study personnel are required to provide their signature, initials, title, responsibility for the study, and start and stop dates. The log is incomplete in that the start and stop dates were not recorded for several of the study personnel. For example, there is no stop date for Dr. ——who left the study in August 2001. As a result, it in unclear who was authorized to participate in the study and make data entries. Moreover, on two occasions an unauthorized person dispensed the investigational product and on at least one occasion an unauthorized nurse administered the investigational product.

In your response letter, you state that you do not intend to amend the FDA form 1572 to list the individuals who dispense the study-related products on a temporary basis. We recommend that you consult the sponsor in this matter to ensure that you fulfill the sponsor's requirements to prepare documentation of the training of "temporary" replacements to assure that the study blind is not compromised

2. You failed to maintain adequate and accurate case histories. [21 CFR § 312.62(b)].

A. The protocol requires that the study drug must be administered to subjects within — minutes after it is thawed. Furthermore, the protocol's "Site Reference Manual" states, "The —-minute window begins **after** the investigational agent is reconstituted. The reconstitution and administration times of the investigational agent **must** be documented in the source" records [bold in the original]. This requirement applied to both the study drug and the skin test. These instructions are repeated in the "Medical Record Documentation" section of the "Site Reference Manual." Documentation was required to assure that the study drugs retained their potency.

However, the times of study drug reconstitution and administration were not documented. We note that the study drug was prepared several buildings away from the clinic where it was administered.

Your response states that the original study forms provided by the sponsor did not specify documentation of these times. However, page 2 of the "Site Reference Manual" section entitled "Documentation of Clinical Trial Data" states:

> Note: The time of preparation and administration of the investigational agent must be documented to reflect that the investigational agent was administered within the — minute time period, once the I.A. [investigational agent] is reconstituted, as stated in the protocol. A

procedure may need to be put in place between pharmacy personnel and the nursing staff. [bold italics in original text (whole note) removed here]

Your response includes the sponsor's revised case report form that has places to record these times. Your response does not explain how the study drug preparation time is transmitted to the person administering the study drug to the subjects. Although the case report form page you provided with your response will document the time that the study drug was administered, you failed to provide the pharmacy record where the person who prepares the study drugs will document the time the study drug was prepared. Please provide the pharmacy record sheet showing where these values are being recorded, and copies of these completed records for the past four months.

B. The lot numbers for the skin test antigens and/or BCG were not documented for several subjects, including — (1/18/00), — (8/19/99), — (4/24/99, 5/3/99). — (8/29/00), —— (12/28/99), and — (10/18/99).

In your response, you state you will document the administration and lot numbers in the future.

C. On several occasions, there is no record of who administered the study drug, including subjects — (1/2/01), —— (11/30/99 and 12/28/99), — (11/30/99). —(1/18/00), — (5/3/99),— (3/14/00) and — (9/26/00). That list is based on a review of a limited number of records and may not be complete. Without a record of who administered the study drug, you cannot assure that these injections were performed by a member of the blinded study team.

Your response letter explains that, throughout the trial, a research nurse administered all test articles and that the revised case report form currently in use has a separate signature line for the nurse who will conduct the study visit assessment and administer the study-related injections. In your response to this letter, please explain how you will supervise the study staff to ensure that study drug injections are properly signed and dated.

D. The protocol requires that corrections to case report form data may be made only by putting a single line through the incorrect data, and then writing the correct data, the initials of the person making the change, and the date. This procedure was not followed on many records, including study visit notes.

In your response, you explain that you have retrained the study staff to properly document changes to study data. In your response to this letter, please explain how you will supervise the study staff to ensure that data changes are properly initialed and dated.

3. **You failed to maintain adequate records of the disposition of the drug. [21 CFR § 312.62(a)].**

A There are discrepancies between the drug accountability records and the source documents in the medical records.

Subject	Date	Test Article Records	Medical Records
———	1/18/00	Lots ———	Lots not recorded
	3/14/00	Lot ———	Lot ———
	6/26/01	Lot ———	
	9/25/01	Lot ———	
———	11/30/00	Lot ———	Lot ———
	1/10/02	None dispensed this date	Lot ———
———	4/24/01 5/22/01	Lot ———	Lot ———
———	12/28/00	No record of this lot	BCG lot ———

Your response attributes these errors to the "initial inexperience" of the person who prepared the study drug, but you do not explain why these discrepancies due to "initial inexperience" still persisted from 1/18/00through 1/10/02, when the study began in 1998. Your response states that new inventory forms provided by the sponsor should prevent similar errors. Your response does not explain how the lot number information is transmitted to the unblended study team, and therefore your response is inadequate to describe how you will prevent such omissions and discrepancies in the future.

B. Some test article accountability records were changed by study personnel who were not involved with test article preparation. These changes include the date the test article was prepared. Many of the changes were made days after the original entry, with no way to verify whether the changes were correct. Sometimes the initials and date were omitted, and sometimes the original data was written over.

In your response, you explain that only the person preparing the study drug is permitted to record test article accountability information. Your response is therefore inadequate to explain how a different person was granted the authority to make such changes. Please explain in detail

your corrective actions to prevent this violation, and how you will supervise the study staff to ensure that the corrective actions are followed.

You are currently involved in more than —— other clinical studies of products regulated by FDA. In your response, please explain how you have evaluated the conduct of each ongoing study to assure that they are conducted in compliance with 21 CFR Parts 312 and 50. Please describe how you will supervise the study staff involved in each study, and your personal role in each study.

This letter is not intended to be an all-inclusive list of deficiencies. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations.

Please notify this office, in writing, within fifteen (15) business days after receipt of this letter, of the specific actions you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Failure to promptly correct these deviations may result in enforcement action without further notice. Please also be advised that the failure to effectively put into practice the corrective actions you have described in your response letter, or the commission of other violations, may result in the initiation of enforcement action(s) without further notice. These actions could include: clinical hold of ongoing studies: initiating investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs; and initiating an action for injunction.

Please send your written response to:

Patricia Holobaugh
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's Baltimore District Office listed below.

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

Lee Bowers, Director
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6000 Metro Drive
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Robert L. Campbell, DDS, Chair
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[redacted]